REMARKS

Claim 1 has been amended to limit the condition being treated to cognitive dysfunction and the compounds used to nicotinic allosteric potentiators. In order to expedite prosecution of the present application, Claims 37 and 39 have been canceled without prejudice to the possibility of pursuing them in continuing application. Claim 40 has been canceled in view of the amendment to claim 1. Claim1 has also been amended to replace the language "other than one diagnosed as suffering from Alzheimer's disease" to "other than one being treated for Alzheimer's disease". In the response of July 5, 2007, the applicant indicated her willingness to accept this alternative language. The final rejection makes no comment on this suggestion.

The examiner questions whether the original disclosure teaches that the present invention does not relate to treating those who have been diagnosed with Alzheimer's disease, but accepts that the specification teaches the prior use of galanthamine for treatment of this disease (see paragraph 8 of the specification). It is therefore clear to one skilled in the art that the present invention does not involve treatment of Alzheimer's disease but rather a totally different condition resulting from low LDL. It is arguable therefore that the applicant should be permitted to claim her invention in such broad terms, even without exclusion of any patients suffering from Alzheimer's disease since the root causes are different. There is, however, a practical problem with a claim of this type since a given patient could be suffering from both conditions and so determining infringement becomes much more difficult. Therefore to make it easier to determine patients whose treatment would be an infringement, the applicant is willing to exclude such "overlap" situations from her claims. As noted above, the present specification clearly did not contemplate reclaiming treatment of Alzheimer's disease with galanthamine. This was the subject matter of the applicant's Patent No 4,663,318 granted over twenty years ago.

It is therefore submitted that claim 1 as presented previously complied with 35 USC 112 first paragraph having regard to the nature of the patients to be treated and *a fortiori* the claim as amended meets this requirement.

So far as the 35 USC 112 paragraph 1 rejection relating to the definition of the active compounds is concerned, the independent claims have been amended to limit these to nicotinic allosteric potentiators (which the examiner agrees are enabled).

It is therefore submitted that the requirements of 35 USC 112 first paragraph have been complied with.

Turning now to 35 USC 112 second paragraph, claims 37 and 39 have been canceled to simplify prosecution. The examiner also lists claims 1, 3-4, and 38 as being rejected under this paragraph but gives no reasons for this rejection.

It is submitted that the claims are clear and that the requirements of 35 USC 112 second paragraph have been met.

So far as the 35 USC 103 rejection is concerned, the claims exclude patients who are being treated for Alzheimer's disease. The examiner's rejection is predicated on the idea that those who suffer form Alzheimer's may also take statins and on the idea that taking statins may reduce the risk of Alzheimer's disease.

The examiner's comment that in assessing obviousness one must place oneself in the position of one skilled in the art at the time that the invention was made is of course correct. However, in the present case, what is accepted now as prevalent view on whether statins would be useful to treat Alzheimer's disease (see for example an article in Business Week for January 28, 2008) there was no reasonable expectation that stains would be useful for treatment of Alzheimer's disease even at the time the application was filed. The examiner's position seems to be based on the teachings of Simons, Jick and Wolzin. These articles and the reaction to them at the time they were published need to be considered more carefully and read in conjunction with the Kivipelto reference.

Before doing this, however, it is worth re-emphasizing that the present invention does not relate to treatment of Alzheimer's disease but to an unrelated problem of how to deal with cognitive dysfunction resulting from low LDL-cholesterol values. Such low values are not necessarily the result of taking statins and as the examiner notes, do not correlate with an incidence of Alzheimer's disease.. Prior to the present invention nothing in the art pointed one towards administering galanthamine or other allosteric nicotinic potentiators to those having low LDL cholesterol values. This is the core of the present invention and was nowhere foreshadowed by any of the cited art.

We can now turn to the state of the art in 2002 when the present application was filed.

To paraphrase page 11 of the action, an elderly patient suffering from a cognitive disorder receiving statins for hypercholesterolemia would be expected to be given galanthamine for the cognitive disorder. This is because Kivipelto taught that high levels of cholesterol are associated with Alzheimer's disease, and that patients with a history of receiving statins for hypercholesterolemia had less Alzheimer's disease (Simons). As will be shown below, this conclusion is not logical and these references provide no reasoning that would point to the present invention.

Kivipelto reports the relationship between *midlife* total cholesterol, as well as systolic blood pressure and body mass index (average age 50.4) and Alzheimer's disease *diagnosed 21 years later,* at an average age of 71.3 (lower right, page 1448) in a Finnish population. During midlife, cholesterol was significantly higher in those destined to get Alzheimer's disease in old age, as compared to those who were not, 7.2 vs 6.7 mmol/l , $p = 0.001$. At the time of diagnosis, there was no significant difference in cholesterol levels between those with and without Alzheimer's (6.0 versus 5.8 mmol/l, $p = .234$). Similarly, significant differences in blood pressure and body mass index at midlife disappeared by the time of diagnosis of Alzheimer's disease. Thus, Kivipelto teaches that high levels of cholesterol in *midlife* are correlated with Alzheimer's disease in the *elderly*.

It can be assumed that at the midlife examination, subjects were overwhelmingly not demented. Medical histories were provided, the patients survived for at least the 11 years from the last midlife exam (1987) until the cognitive testing (1998), and Alzheimer's disease is extraordinarily rare at age 50, occurring only in a few families with certain genetic mutations. Thus Kivipelto is not teaching the administration of statins in the presence of dementia, but that treating hypercholesterolemia in *midlife* to nondemented people "may have implications for the prevention of dementia," occurring in the *elderly*. Statins used in this way for the possible prevention of dementia would be given decades before the expected onset of dementia.

Kivipelto et al may not have been more definite about recommending hypercholesterolemia treatment because treatment had no effect on the development of Alzheimer's disease in their population. Ten of 48 (21%) of Alzheimer's disease patients had received cholesterol lowering agents, while 208 of 1352 (15.4%) nondemented subjects had been treated with the drugs. The higher percentage of treatment in the Alzheimer group was not statistically different from that in the nondemented group (table 3, page 1449). The Applicant agrees with the Examiner that treatment was assessed at the time of re-examination. However, Table 3 does not support the statement that at the bottom of page 4 of the office action that "the data is merely teaching that of the 218 people receiving cholesterol lowering therapy, there is a lower incidence of patients having AD."

The table itself indicates that 21%, or 1 out of 4.8 patients with Alzheimer's disease were receiving cholesterol-lowering drug treatment. Only 15.4%, or 1 out of 6.5 non-demented subjects were receiving a cholesterol-lowering treatment. So there was *more* cholesterol treatment in the group with Alzheimer's disease than in controls, although the numbers were not statistically significant. Another way of looking at the numbers, as was done in the prior response, is to say that of the 1400 (48 with AD and 1352 without) subjects, 218 were on cholesterol treatment and 1182 were not. Ten of the 218 (4.6%) on treatment, and 38 of the 1182 (3.2%) on no treatment had Alzheimer's disease. By this method, there was a *higher,* not a *lower* incidence of Alzheimer's disease in those receiving cholesterol lowering agents.

Contrary to the examiner's position therefore this teaching does not clearly lead one to conclude that one should treat Alzheimer's disease by use of statins and consequently it does not teach one to treat anyone with combination of an Alzheimer's drug with a statin.

The present invention includes treatment of a statin-induced cognitive disorder. Such disorders were recognized across the country in the lay press (Graedon T, Graedon G. The people's pharmacy. Los Angeles Times. May 22, 2000, health section: S2, S6 – this is reference 8 in Golomb, 2001, see below), reported at conferences (King DS et al, Cognitive impairment associated with atorvastatin, Pharmacotherapy 2001; 21(3):371, in a 67 year old woman from Mississippi) as case reports (Orsi A, Simvastatin associated memory loss, Pharmacotherapy 2001; 21(6):767-769, in a 51 year old man from New York), in letters to the editor (Golomb BA, Arch Neurol 2001; 58:1169, reporting receipt of "dozens of written reports" in California), in randomized clinical trials (Muldoon, 2000 and Roth abstract, 1992), and from abroad (Australian Adverse Drug Reactions Bulletin 1998; 17(3):11, describing the case of an elderly man who developed memory loss after two weeks on simvastatin with improvement on discontinuation and recurrence on retreatment, as well as noting 14 reports of statin-induced amnesia, the second highest of all drugs causing this problem). Discontinuation of the statin was reported to solve the problem in these cases, and in those who were rechallenged, the cognitive dysfunction recurred. Nothing in the art would point to use of an Alzheimer's drug to treat such disorders. The examiner has given no basis for thinking that the pathology to be treated is the same and hence no reason for taking a drug that is used for one condition and applying it to the other.

Notably, some of the patients reported, for example in the King abstract and the Australian Adverse Drug Reactions Bulletin have statin-induced cognitive dysfunction were elderly. In these patients, the drug adverse reaction was identified and differentiated from other causes of cognitive impairment. In view of the last phrase in the office action on page 11, that "one would have a reasonable expectation of success with treatment of galanthamine for a cognitive disorder", it should be appreciated that "cognitive disorder " can be caused by many processes. Doctors faced with a patient with a cognitive disorder evaluate the patient with a history, including medications, a physical exam, laboratory tests, imaging studies, and psychological testing, as indicated. They may also follow the patient for a time and retest.

They may find any number of underlying conditions, such as progressive dementias (Alzheimer's and others) endocrine abnormalities (hypothyroidism, hypoglycemia), nutritional deficiencies (vitamin B_{12}), infection (brain abscess), structural abnormalities (brain tumor, normal pressure hydrocephalus), psychiatric disease (pseudodementia), drug side effects (in addition to simvastatin, the Austrialian Adverse Drug Reactions Bulletin listed sertraline, paroxetine, midazolam, dothiepin, moclobemide, fluoxetine, ranitidine), to name some of a long list of possible causes. If the diagnosis is Alzheimer's disease (the diagnosis of which requires the absence other treatable causes of dementia), then galanthamine may be used. However, there would be no expectation of success in using galanthamine for an undiagnosed cognitive disorder, and it is not medical practice to do so.

In the reported cases, the relationship between cognitive loss and statin use was identified and the statins were discontinued. This simple maneuver made it possible to differentiate this cause of cognitive dysfunction from other causes of cognitive dysfunction. Discontinuing the statin may even identify that a statin-induced dementia exists along with another cause of dementia. However, discontinuation of a treatment that is normally prescribed to try to avoid heart disease or stroke is not normally a good option. The present invention provides a much preferable alternative by use of a nicotinic allosteric potentiator.

The Applicant notes that statin-induced cognitive dysfunction can be identified in a group of AD patients treated with galanthamine or placebo, each with and without statins. Three 5 to 6 month studies on the efficacy of galanthamine, 24 mg/day, versus placebo, were combined to assess the effect of concurrent statin administration. These studies were conducted in the late 1990s, and published individually in 2000 and reported as references 16, 17 and 18 of the Winblad reference (i.e Raskind et al "Galantamine in AD: a six month reandomized, placebo-controlled trial with a six month extension"; Tariot et al "A 5-month randomized, placebo-controlled trial of galantamine . in AD"; and Wilcock et al. Efficacy and safety of galantamine in patiemts with mild to moderate Alzheimer's disease: multicenter randomized controlled trial. Patients met standard criteria for the diagnosis of AD and were randomized to galanthamine or placebo. Of the 1325 patients, 92 were receiving statins on entry and continuously throughout the study. Statin use was not randomized, it had been prescribed prior to the study.

The patients were divided into 4 treatment groups, statin plus galanthamine (n=42), statin alone (n=50), galanthamine alone (n=614), and neither statin nor galanthamine (n=619). At baseline, cognitive scores and cholesterol levels did not differ among the groups. The statin patients were significantly younger, 72.0 and 74.0 years old, than those not receiving statins who were 75.7 and 75.2 years old (p=.045). The percentage of females was smaller, although not significantly so, 47.6% and 58%, as compared to 66.3% and 66.0% (p=.063). Over the course of the study, there was no difference in deterioration in the patients receiving only statins (1.98±.91 points on the ADAS-cog), as compared to those on neither statins nor galanthamine (2.24±.24 points). (On the ADAS-cog scale, positive scores are deterioration and negative scores are improvement.) Statin-treated patients who were randomized to galanthamine, however, had a significantly larger improvement on drug (-2.85±.91 points) than those not on statins who were given galanthamine (-0.88±.25 points). Thus, galanthamine had an additional effect in patients receiving statins which was not present in patients not receiving statins.

The statin-treated patients with Alzheimer's disease had two causes of cognitive impairment. As was known at the time, the neurons making acetylcholine were degenerating from Alzheimer's disease. However, there was a second factor, hitherto unknown the realization of which led to the present invention, namely that the nicotinic receptors were dysfunctional because of cholesterol depletion by statins As noted in response to the previous action, the applicant's inventive **insight lay** in appreciation of the relationship of the clinical consequences of cholesterol depletion with nicotinic receptor function, and the substantial benefit to be obtained as a result of augmenting that receptor function. Galanthamine, because it is an inhibitor of acetylcholinesterase, the enzyme which destroys acetylcholine, and an allosteric enhancer of nicotinic receptors, was able to ameliorate both conditions. The addition of two reasons for cognitive impairment may explain why statin-treated patients entered the study at a younger age, as impaired as older subjects not on statins. Their apparent larger response to galanthamine is consistent with treatment of both their statin-induced impairment and their Alzheimer's disease. It should, however, be noted that this conclusion was based on a simple t-test using the means and standard deviations of the cognitive effect of the two conditions. Winblad et al used an analysis of variance. The variables used are not relevant to the applicant's insight. According to that insight (that low cholesterol and in particular such a condition as a result of the use of statins(affects the nicotinic receptors. With this insight, it does not matter, for example, how demented a patient is to look for the statin effect. It mattered to Winblad et al because if you are looking for an effect on progression, that might be apparent in milder patients but not in those too far gone. The Applicant therefore noted a significant effect, while Winblad, who added covariates relevant to their hypothesis, missed statistical significance.

Wolozin

Although Kivipelto, in table 3, provided evidence that cholesterol-lowering treatment at the time of diagnosis did **not** alter the incidence of Alzheimer's disease, the two references cited in Simons, Wolozin and Jick, did claim a statin effect.

In the response filed on July 5, 2007, the applicant pointed out the shortcomings of these studies. The applicant now wishes to direct the Examiner's attention to contemporaneous publications which made many of the same, and additional points.

The Wolozin paper was published by the Archives of Neurology because, in their words, it was provocative. The summary on page 1409 of the journal issue states:

> "Wolozin and colleagues (page 1439) report a lower prevalence of diagnosed probable AD in patients taking 2 different HMG-CoA reductase inhibitors, lovastatin and pravastatin. A similar effect was not found with simvastatin. The findings are provocative and thus reported as an Archives Express publication. These data will be substantial only with prospective rigorous clinical trial as proposed by the authors."

The Archives then went on to provide a commentary in the same issue, not willing to let the assertions of the Wolozin paper go unchallenged for any period of time. Haley and Dietschy, in their editorial, first provide biological plausibility – reviewing cholesterol metabolism in the brain and its relationship to the Alzheimer's amyloid. But a greater portion of the editorial questions Wolozin's methodology and teaches that any relationship between statins and dementia prevention must be answered by randomized, prospective clinical trials, not by reviews of data sets in which people with low risk factors for Alzheimer's disease were more likely to have been prescribed statins. Haley and Dietschy state (p.1411 starting with the first full paragraph):

> "On the other hand, the statistical association presented by Wolozin and colleagues, though strong and highly statistically significant, cannot yet be considered a causal one because of 2 complicating issues: first, the inconsistency of effect among different statins; and second, the likelihood of confounding by indication of statin therapy ("indication bias"). In their analysis the authors found that the prevalence rates of AD were lower in patients taking lovastatin, pravastatin and the combination of lovastatin plus pravastatin than in patients taking other types of medications, but the prevalence rate in those taking simvastatin did not show the same effect. Given the large numbers of subjects studied this disparity in effect among the statin drugs was highly significant (P<.005) and thus probably not due to chance alone. Since the magnitude of the lipid-lowering effect of simvastatin is not appreciably different from that of the other two statins, this finding

suggests either that lovastatin and pravastatin prevent AD by a mechanism other than reducing cholesterol biosynthesis or that differences in the usage patterns of the 3 drugs are somehow colinked with indication bias...

"The real problem in the interpretation of the study is the possibility that the association actually has a trivial explanation related to possible differences in prescribing practices involving the statin drugs in patients with and without early AD. Confounding in analyses of the efficacy of drugs by the indications for which they are prescribed is a powerful type of selection bias well recognized in the field of pharmacoepidemiology. Known as indication bias, it is a common explanation for why observational studies of drug effects often give wrong answers and why prospective, randomized, double-blind, placebo-controlled clinical trials are required to establish treatment effects....In this circumstance , the only way to disentangle the true causal effects from indication bias is by performing a formal randomized clinical trial.

"There is a plausible set of circumstances in which indication bias could explain the authors' findings. Cross-sectional in design, the study selected patients who received care in any of the 3 hospitals from October 1, 1996, through August 31, 1998, and defined both medications and AD from computerized medical records. During the early to mid 1990s when many of these patients would have begun statin drug therapy, only a small percentage of patients with elevated serum cholesterol levels received statin treatment; national recommendations discouraged statin treatment of the elderly (aged >60 years) for 3 reasons: First, there is a lack of studies in this age group. Second, the assumption (later dispelled) that prevention required many years of therapy with its concomitant economic considerations. Therefore, it is plausible that during that era, *physicians were more likely to prescribe statins to those elderly patients who asked for statin treatment, who could afford to pay for it, and who were compliant with dietary and medication regimens. These would have been the patients who were more highly educated, affluent, inquisitive, and concerned about their future health. Finally it is well known that a state of reduced cognitive function and inability to plan for the future often precedes the formal diagnosis of AD by many years, the so-called pre-dementia phase.* The net effect of these influences – physicians being less likely to prescribe statins for patients who would later be diagnosed with AD – would explain the apparent protective effect of lovastatin and pravastatin for AD presently being reported." [Emphasis, in the form of italics, added]

The authors go on to propose that simvastatin might not show the association with reduced diagnoses of AD because it came to be widely used later than the other drugs, "after statin therapy had become more liberally prescribed in older age groups." They conclude (bottom of second column on page 1411) "The report of Wolozin et al has therefore presented important epidemiologic data to focus the attention of the scientific community on the question of whether statins can prevent AD, but it has not

proved the causal nature of the association...Because AD is not a reversible disease, statistical approaches for disentangling true effects from bias in observational drug studies are not applicable to this problem, and only observing groups of patients randomized to statin treatment and placebo will provide a definitive test."

Thus the Archives of Neurology, at the same time as it publishes a paper claiming that statins prevent Alzheimer's disease, disputes the methodology of the paper. It suggests that statins at the time may have been given to an educated, affluent, inquisitive , intellectually competent group of patients who, for those reasons, was less likely to receive a diagnosis of Alzheimer's disease. Patients diagnosed with Alzheimer's disease , on the other hand, would have previously been in a prodromal state called "Mild Cognitive Impairment" (MCI).

Identification of mild cognitive impairment was the subject of a "Practice parameter" of the American Association of Neurology in 2001 (Peterson R et al, 2001; 56:1133-1142) Peterson et al review studies of patients with mild cognitive impairment,having a duration of 2-6 years, which show conversion rates to Alzheimer's disease averaging 12-15% a year. "By 6 years, approximately 80% of the individuals had developed AD." (bottom left, page 1136). A common test used to make this diagnosis is the clock drawing test, in which the patient must have the "ability to properly draw the face of a clock by appropriate placement of the numbers and the hands of the clock to a designated time." (page 1139, middle left). In another task, patients are asked to read the time from a clock and set it to a designated time. The MiniMental State Exam asks patients to follow simple commands, remember three words over time, subtract 7 from a hundred repeatedly, demonstrate orientation to time and place. The Clinical Dementia Rating (CDR) is also used. It assesses "orientation, judgement, memory, community affairs, personal care, and home and hobbies." (page 1140; bottom left)

The Wolozin study covered about a two year time period. Haley and Dietschy point out that patients obtaining statins were educated, informed, actively interested in their health care, all factors which would diminish the incidence of Alzheimer's disease.

Patients receiving a diagnosis of Alzheimer's disease had for several years, at least, difficulties in everyday tasks that would make it much less likely for them to have learned about statins and prevail upon their physicians for a prescription. These differences were likely able to account for the lower incidence of Alzheimer's disease in patients on statins. The one statin which did not show a difference was a latecomer which may have been prescribed more broadly. Only a study in which statins were administered randomly and blindly could address the important question of whether they could prevent AD.

The impressions in the editorial were echoed repeatedly in Letters to the Editor of Archives. Lesser and Libow (Arch Neurol 2001; 1023) comment "The presence of confounders could be important to the observed associations. It is likely that the relatively new, costly statins were utilized most often by sophisticated, more alert, better educated people; such persons are at a lower risk to develop dementia." Wolozin et al agree that "the absence of any association between simvastatin and AD in our data set could indicate the presence of confounding variables producing either positive or negative spurious associations. Such variables could lead to a spurious positive association between pravastatin or lovastatin and decreased prevalence of AD, or to a spurious negative association and decreased prevalence of AD." Lesser and Libow then cite Jick, which will be discussed below. In response to the letter, Wolozin et al do confirm Haley and Dietschy's hypothesis that simvastatin may have been the latest statin to be available. (page 1023) Bollen, Gaw and Buckley comment that the statin/decreased prevalence of AD may have been due to confounding variables, such as clinicians not differentiating AD from vascular dementia. They note Wolozin et al's stressing the need for a rigorous prospective trial and indicate that their trial of pravastatin, which includes cognitive testing, will be available in 2002. The absence of information on potential confounding factors such as education and/or income, was noted by Muldoon, who re-emphasized Haley and Dietschy's point regarding statin administration to particularly healthy individuals.(Arch Neurol 2001; 1166) Golomb and Jaworski suggest that very high cholesterol could protect against AD, and "those on statins may (before treatment and often despite treatment) have higher cholesterol levels on average." Thus statins would only be a marker for patients with very high cholesterol. The reason simvastatin

was not protective against AD, therefore, in their view was that it was the most potent of the statins and would have lowered cholesterol the most. (Arch Neurol 2001; 58:1160)

Jick

Jick et al performed a nested case-control study in which patients with dementia were matched to controls based on age, sex, clinical practice and index date of case. The dementia was not limited to Alzheimer's disease, education levels were not controlled for, and lipid levels were not provided. Patients were followed from 1992 to 1998. Patients receiving statins had a markedly reduced relative risk for dementia, 0.29. Patients with untreated hyperlipidemia had a nonsignificantly reduced risk, 0.72 ($p = .016$). The authors readily consider the possibility that "patients who received statins were selected with regard to level of education, socioeconomic status, and cholesterol, which themselves may be linked to the risk of dementia. Information on these variables was not available." (p 1629) They also note that "many observational studies provide results which are not causal. Indeed, they may be spurious. The explanation for such findings is regularly due to problems with epidemiological technique." They then cite the conflicting results in studies of estrogen in Alzheimer's disease. (p 1630)

Comments on the Jick article were similar to those directed to Wolozin et al, although by different parties. Birkenhager, Wand and Staessen write

> "...Jick and colleagues mention the possibility that the reduced risk for statins could be caused by characteristics of the statin recipients that are associated with a lower risk of dementia. They should have expanded this point, since they were close to touching on the fundamental weakness of the study: bias by indication. Sociological experience shows a group of intelligent, well informed, alert, mostly urban patients. If they develop hypercholesterolaemia, they frequently demand and obtain the most modern lipid-lowering agents. By contrast, other patients, generally of lower socioeconomic status, are less aware of cardiovascular risk factors and treatment trends. In the Systolic Hypertension on Europe trial, age on leaving school was a major determinant of cognitive function, measured by the mini-mental state questionnaire.
>
> "This type of pre-ordained selection might partly explain the negative association between dementia and the use of statins, rather than a pharmacological action of this drug class." (Lancet 2001; 357:880)

Cheung and Kumana note that the proportion of dementia cases receiving statins is "strikingly low," and that "A person who has dementia is much less likely than someone without to be prescribed statins." They congratulate the authors "on highlighting an

important imbalance in the prescription of statins. If it is confirmed, what should be debated is whether statins should or should not be withheld from people with dementia." (Lancet 2001; 357:880)

Table 3 in the Jick paper (p 1628) provides support for the assertion that compromised patients did not receive statins. In controls, statin use increased from 21 to 83 patients (395%) from the period 2-4 years prior to the index date, to the period < 2 years from the index date. Over the same periods, statin use in the demented group increased only from 5 to 6 patients (20%). This lack of increase in the use of statins as the diagnosis of dementia drew near is consistent with the concept that it was the developing dementia that decreased statin prescriptions rather than the lack of statins facilitating dementia progression. This is the essence of indication bias: the reason statins are withheld is the developing disease itself.

Blauw, Shepherd and Murphy note that the pravastatin trial, which is double-blind, randomized, and placebo-controlled, will be available in 2002. (Lancet 2001; 357:881)

Ebrahim, Ben Shlomo, Davey Smith, Whincup and Emberson advise caution in interpreting Jick. They felt the 13% incidence of untreated hyperlipidemia was not consistent other databases and that patients must have been misclassified. (Lancet 2001; 357:882) They were also surprised by hyperlipidemia's being associated with, "if anything, a decreased risk of dementia, contrary to findings of prospective studies." They too noted that

> "Patients of lower socioeconomic positions might be less likely to be screened and treated with newer drug regimens. Since dementia is strongly associated with education level, the observed relation with statin use might be confounded by differential misclassification of hyperlipidaemia and treatment with statins. Jick and colleagues control for various potential confounders, but not for socioeconomic position or education level."

Using data from the British Regional Heart Study and the British Women's Heart and Health Study, Ebrahim et al calculated the effects of misclassification of hyperlipidemia and differential use of statins by educational level on the odds ratio for dementia. The hyperlipidemia calculation, "equivalent to that which may have occurred in Jick's study, suggests a large but spurious protective effect of statins....Differential use of statins by

educational level generally increased the apparent protective effect of statins." They call for "large, randomized controlled trials of statin use."

MacMahon and Collins

In a review on observational studies, the authors advise caution when "the most plausible expectation of benefit is that a treatment produces only moderate (although still potentially worthwhile) effects on serious outcomes. For the reliable assessment of such effects of treatment, observational studies have a much more limited part to play, since the potential biases could obscure, inflate or even seem to reverse the real effects of treatment – and these biases cannot be quantified reliably." (p 456, middle left) They cite case-control evidence that angiotensin converting enzyme inhibitors reduced cancer, an effect not confirmed in large randomized trials. For hormone replacement therapy in women, reported associations with less coronary heart disease and colorectal cancer could have been due to biases such as the "preferential prescription of hormone replacement therapy to lower-risk women," and its effects "would only be known when results emerge from large randomized trials."(p 456, middle left) (See the section on Rockwood in which the randomized trials showed an *increased* risk of heart disease.) The paragraph ends "Similarly, the observation in a case-control study of a 70% lower risk of dementia among individuals treated with statins cannot be accepted as good evidence of benefit from the treatment," citing Jick et al, Lancet 2000; 356:1627-31.

Rockwood

Rockwood et al performed a secondary analysis of data from the Canadian Study of Health and Aging, the purpose of which was to look for any relationship between lipid lowering agents and dementia, and to identify indication bias, that "people who elect to take lipid-lowering agents (LLAs)may be healthier than those who do not, so that it may be these other health factors that explain their lower risk of dementia." (p 223, upper left)

The population consisted of 2305 people, including 492 incident cases of dementia, who received cognitive testing using the 3MS (Modified Minimental State Exam) in 1991-2 and again in 1996. Cholesterol was not measured, but dementias were further diagnosed as

Alzheimer's disease (326) or other dementias (166). Very few subjects were on treatment : 17 on statins and 14 on other agents in 1991-2 (CSHA-1) and 57 on statins, 15 on other LLAs in 1995 (CSHA-2).

The significance of the effect of statins or other LLAs was a function of whether potential confounders were considered. An unadjusted analysis showed a significantly lower odds of AD and all types of dementia in users of statins or any LLA. When stratified by age, the effect of a statin or an LLA remained only for those younger than 80 years, and then only for all types of dementia. When sex, educational level, and self-rated health were added, the association of statins or LLAs with all types of dementia remained, but in those "80 years and older, the CI (confidence interval) includes 1.0," indicating that there may be no protective effect. Thus, the initial impression of a significant relationship between statins and protection against Alzheimer's disease disappeared when age, sex, educational level and self-rated health were considered. An association between dementia and a reduced use of statins could be restored by including institutionalized subjects, who have a "high prevalence of dementia but who were infrequently taking statins." (p 225, lower left) This indicates how easily indication bias, in this case, giving statins to those who were cognitively competent enough not be be in nursing homes (most nursing home patients have dementia) and withholding statins from those in nursing homes can create a spurious association between statin administration the lack of dementia.

This study validates some of the confounders, suggested by Haley and Dietschy and various letter-writers, that are present in a short-term (4-6 year) study of the relationship between statins and Alzheimer's disease. The most striking finding is that 32% of those with AD at the 1996 evaluation, but only 5% of those with no cognitive impairment, had had "cognitive impairment, no dementia" (CIND) at the 1991-2 evaluation. This is consistent with the mild cognitive impairment studies showing impairment 4-6 years prior to the diagnosis of AD, with conversion at 12-15% a year. When patients with cognitive impairment in 1991-2 were eliminated from the analysis, the relationship between statin use and incident dementia lost significance, as the 95% confidence interval included 1.0 (OR 0.36, 95%CI, 0.11-1.23), a finding the authors attributed to reduced numbers. (p 226, lower left) AD patients were also five years older, (81.2 vs 76.0), more likely to be female (70% vs 58%), less educated (9.2 vs 10.3 years), and less likely to live in the community (87% vs

94%). Except for educational level in this cohort, statin users had the opposite characteristics: they were younger (70.3 vs 78.3 years), less likely to be female (53% vs 62%), and more likely to live in the community (100% vs 86%) than patients taking neither statins nor LLAs. The significances of those comparisons are not given, as Table 1 gives significances only for a different comparison. (p 225)

Thus, the confounders which Rockwood et al chose to correct for, age, educational level and self-rated health, did not affect the significant relationship between the use of statins and other LLAs and the risk of Alzheimer's disease in patient less than 80 years old. When the additional confounder of baseline cognitive impairment was added, significance was removed. Most of the statins used in this study were prescribed after the starting date. Seventeen of the 57 statin patients were treated at CSHA-1, therefore the other 40 received new prescriptions during the four years of the study. These were less likely to go to older females, and most probably to those who were too impaired to request them.

The authors discuss confounding by indication in observational studies and cite the case of estrogen. Postmenopausal estrogen, in observational studies, decreased the risk of dementia by 29%, but had no effect in subsequent randomized, controlled trials. There were similar findings from observational studies of estrogen and ischemic heart disease in women. "In contrast, randomized treatment trials, again, have not shown a protective effect. Moreover, the ongoing Women's Health Initiative, a randomized clinical trial of 27,500 healthy women, recently issued a press release to communicate an early finding of a small increase in heart attacks, strokes, and blood clots in women taking hormones compared with nonusers." (p 225, lower right).

The authors advise caution in the interpretation of their data, saying that they addressed known risk factors, but "cannot account for unknown or unmeasured factors." (p 225, lower right) The authors believed their data were supportive of a protective association between statins and dementia, but acknowledged that "longitudinal studies investigating the link between hypercholesterolemia and AD give conflicting results, the tantalizing possibility that LLAs might help to prevent dementia requires further research.

Yaffe

Yaffee et al have done a reanalysis of data derived from a 4 year study of estrogen versus placebo in 1037 women with established coronary heart disease. As noted by Rockwood et al, Yaffee et al's study was one of the randomized, controlled studies of administration of estrogen that showed that the observational studies suggesting estrogen was protective against heart disease were wrong. Yaffee et al comment on the Jick and Wolozin papers:

> "Two recent observational studies, one case-control and one nested case-control, reported a 60% to 70% lower odds of developing dementia among statin users. Serum lipoprotein levels were not measured directly in either study and, therefore, it is uncertain whether the protective effect of statin use was related to lipoprotein level or whether the effect was due to an unknown selection bias. However, in their study, Jick and colleagues found that the medical record diagnosis of untreated hyperlipidemia was not associated with a risk of developing dementia. Our goal was to determine if statin use is associated with cognitive function and risk of cognitive impairment in older women without dementia and, if so, if it is mediated by lipoprotein level."

Subjects did not have dementia at entry. Cognitive testing was done only once, at the end of the study. Impairment was defined arbitrarily as 1.5 standard deviations below the cohort mean of the Modified Minimental State Examination (3MS). No attempt was made to diagnose Alzheimer's disease. Women in the highest quartile for LDL cholesterol had poorer performance on the 3MS as compared to those in the lower 3 quartiles. Adjustment for age, educational level, treatment group (estrogen or placebo) diabetes, health status, CABG (coronary artery bypass graft) surgery and aspirin use did not change the results. *"Adjusting for statin use also did not change the magnitude or statistical significance of the results."* (p 380, middle right, emphasis in the form of italics added)

Women whose lipoproteins increased during the 4 year trial also had lower 3MS scores, a finding which did not change after adjustment for the confounders listed above. *"Further adjustment for statin use did not change the results."* (p 380, lower right, emphasis in the form of italics added)

Women in the highest LDL and cholesterol quartile were almost twice as likely to be cognitively impaired, a finding which was still significant after adjustment for baseline characteristics (age, educational level, estrogen or placebo group, diabetic and health statuses, CABG surgery and aspirin use). *"Additional adjustment for statin use did not change the magnitude or statistical significance for any of the analyses."* (p 380, lower right – emphasis in the form of italics added).

Statin use was not randomized. Fifty-six percent of the women received statins. They were more educated (12.9 vs 12.5 years, p=.02), tended to smoke less (10% vs 15%, p=.01), and were more likely to have undergone CABG surgery (43% vs 37%, p=.05). These comparisons confirm statements in Haley and Dietschy's editorial, and multiple letters, that statins at that time went to the better educated and those who were more astute about their health and obtained the newest treatments, such as CABG surgery. All of these characteristics of non-randomized statin-users would be less likely to be found in patients with pre-Alzheimer's mild cognitive impairment. Statin users scored slightly, but significantly better on the 3MS than nonusers (93.7±6.1 compared with 92.7±7.1, i p=.02), but only when the variables differentiating them from nonusers were not considered. The cognitive difference was not a function of cholesterol levels, as covarying for this did not change the significance, but when educational level, smoking and a history of CABG surgery were among the variables in the calculation, te relationship between statin and cognitive status became nonsignificant (p=.09). Cognitive impairment of any sort, as indicated by a low 3MS score, was numerically lower in the statin group (OR, 0.67), but was not significant as the confidence interval included 1.0 (CI, 0.42-1.05), moreover this number was not adjusted for the statin-specific baseline variables The use of nonstatin cholesterol-lowering drugs, which were much older and cheaper, "was not associated with an adjusted odds of having cognitive impairment (OR, 0.97; 95%CI, 0.36-2.61)." (p 382, middle left)

The authors note, "...our study does not specifically address the efficacy of statins for the prevention of AD." (p 382, middle right). In their discussion, they question whether the statin effect on cognition is due to cholesterol lowering, as it was not reduced by covarying

for cholesterol, as it was by accounting for demographics and healthcare, and because they "along with others, did not find an association between non-statin lipid lowering drugs and the risk of cognitive impairment." (p 383, upper left) They consider that some other possible effects of statins might explain the association with slightly better cognitive performance, or that their results could be due to factors such as the study having been done in women with known coronary heart disease. "Finally," they note "because statin use was not randomly assigned to women, and although we statistically adjusted for those characteristics that were different among statin and non-statin users, it is possible that the differences in cognitive function were due to unmeasured confounders. Randomized controlled trials of statins are necessary to determine if they protect against cognitive decline." (p 383, lower left)

Their abstract concludes "The association between statin use and better cognitive function in women without dementia requires further study." (p 378, middle right).

The papers noted above present five studies relating lipids and dementia published just before the priority date of this application. All of them were observational, none was a prospective, randomized, controlled study of the question of a possible preventive effect of statins on the development of Alzheimer's disease. The first, Wolozin, was published explicitly because it was provocative, plausible and potentially important. The editors balanced its contentions with an editorial showing its internal inconsistency, that two statins worked but one didn't, and raised the prospect of bias by indication. (They did not note the 96.3% reduction of AD in treated females in one center. The notion that statins almost completely prevent AD in women would have been seen as absurd, even at that time.) They suggested that the indications for the administration of statins when they were first introduced included having a privileged patient, one who was educated, affluent and influential on his physician and less likely to get Alzheimer's disease. They pointed out that a period of cognitive impairment preceded the diagnosis of Alzheimer's disease, during which patients were less likely to be aware of and to receive a cutting-edge medication. (This period of time was at the time being established officially as mild cognitive impairment.) Numerous letters reiterating these points and the dangers of observational studies followed.

Data from the subsequent studies bore out notion of bias by indication. Thirty-two percent of the patients in Rockwood et al destined to develop AD were documented to have cognitive impairment at entry into the study. Alzheimer patients in the Jick study took statins at roughly the same rate as controls until two years before diagnosis, when the rate of new prescriptions dropped off precipitously. Statin patients were younger, more likely to be male, and more educated in most studies, all factors mitigating against a diagnosis of AD. When these factors were used as covariates, apparent relations between statins and dementia weakened statistically or disappeared. Thus, cognitively stronger patients were more likely to get statins and less likely to get Alzheimer's disease, while the reverse was true for those who were deteriorating mentally.

No study which covaried for demographic factors associated with increased statin prescribing showed a significant relationship between the use of statins and prevention of Alzheimer's disease when covariates were applied in its entire population. (check this) When dementia as a whole was considered, it was suggested that the effect was due to a reduction of vascular dementia by statins. In some studies, high cholesterol was associated with cognitive impairment, in some, untreated lipidemia appeared protective.

The Alzheimer field had seen epidemiologic leads before. Estrogen, long thought to be protective in women, had just been demonstrated, when subjected to a randomized, controlled trial, to be without effect. There was going to be skepticism of an antidementia effect of statins until they were subjected to a controlled trial, which was advised by all the investigators and commentators.

It is therefore clear that at the time of the present invention there was no accepted correlation between statin use and treatment of Alzheimer's disease which is the basis postulate for the examiner's view that one would have combined treatment of a patient suffering from Alzheimer's disease with an Alzheimer's drug and a statin. However, even if that postulate had been established it would not have led to the conclusions drawn by the examiner. As noted in previous responses, the more logical conclusion would be to treat those with high cholesterol with an Alzheimer's drug. Not those with low LDL-cholesterol.

The examiner refers to *in re Kerkhoven* for support for the idea that it is obvious to combine two things that have been taught individually in the art. However, the relevant quote from *Kerkhoven* seems to be

> It is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is to be used for the very same purpose.

The invention related to mixing components together to form a detergent composition. The present invention does not relate to compositions and does not relate to an invention having the same purpose as the prior art methods. Furthermore, treatment of a patient and the interactions of different treatments on patients is a much more complex matter than making a detergent such that what may be logical when combining components for a detergent is not necessarily logical when looking at medical treatments.

More important, however, is that the present invention does not relate to treatment of Alzheimer's disease so that whether or not it is logical to combine statins with an Alzheimer's drug for treatment of that disease is irrelevant to the question of whether there is any logical reason to treat cognitive dysfunction caused by statins with a nicotinic allosteric potentiator. It is submitted that there is no such logical reason. Just because galanthamine and other nicotinic allosteric potentiators may demonstrate a beneficial effect on cognitive problems caused by Alzheimer's disease, it does not follow that they would be expected to he useful in treating other types of cognitive dysfunction and in particular cognitive dysfunction caused by low LDL- for example as a result of treatment with statins.

In view of the foregoing, it is submitted that this application is now in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

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